REMARKS/ARGUMENTS

Claims 5, 9, 10, 11 and 14 have been amended. Claims 18 and 19 have been added. Claims 5 and 7-19 are pending. Claims 5 and 7-16 stand rejected.

Claim Objections

Claims 5, 9, 11 and 14 stand objected to for not referring to the recited sequences by SEQ ID NO. The objection is obviated by amendment of the claims to comply. Reconsideration is requested.

Claim Rejections--35 USC 112, second paragraph

Claims 5, 7-16 stand rejected under 35 USC 112, second paragraph on various grounds.

Second paragraph rejection of claims 5, 7 and 9

Claims 5, 7 and 9 are rejected on the basis of lacking clarity as to the purpose of the process. The rejection is traversed on the basis that statement of purpose is not a statutory requirement, but the rejection is deemed obviated by the above amendment. Claim 5 has been amended to recite in the preamble that the process is "for detecting toxins". New claim 19 also contains this limitation, and claim 7 inherently includes it. Claim 9 has been amended to recite in the preamble that the method is "for numerically assessing the neutralizing potency of a specific anti-serum against a toxin for which it is specific". Determining the neutralizing index for the anti-serum permits its potency to be numerically compared to the potency of other anti-serums which are specific for the toxin, without the killing of large numbers of laboratory animals. The added limitation is submitted to be fairly supported by the claim as written, and by Example VI of the application as filed. Since the rejected claims have been amended for greater clarity as to purpose, reconsideration is requested.

Additional second paragraph rejections of claim 9

Claim 9 is further rejected under 35 USC 112, second paragraph, on the basis of (a) lacking clarity as to how neutralizing potency is determined, (b) lacking clarity as to how numerical assay values are predetermined, (c) lacking of clarity in reciting "toxin assay is determined by ELISA", and (d) lacking clarity as to how anti-LTNF reacts with free toxin in first test since first test uses normal serum.

As to point (a), it is pointed out that the claim as a whole, particularly as amended, clearly describes how the neutralizing potency is determined. Claim 9 recites:

> "determining a neutralizing index for the anti-serum against the toxin, said neutralizing index being given by the difference between
>
> > (1) a numerical assay value for a predetermined amount of a toxin in a normal serum in a first test, and
> >
> > (2) a numerical assay value for a mixture of the predetermined amount of the toxin plus a predetermined amount of the specific anti-serum in a second test,"

and explains:

> "wherein for a given toxin, a higher neutralizing index is indicative of a greater potency for the anti-serum.

The claim thus describes how neutralizing potency is assessed.

As to point (b), the stated grounds is not on point because it is not directed toward the language of the claims, which recite "a numerical assay value for a predetermined amount of a toxin..." and
"a numerical assay value for a mixture of the predetermined amount of the toxin plus a predetermined amount of the specific antiserum".

As to point (c), ELISA assay is well known and needs no further explanation. In any event, the claim recites "the numerical assay values in both the first test and the second test are given by ELISA color assay".

As to point (d), the rejection is not based on the language of the claim, which recites "toxin in a normal serum"in the first test and that the recited antibody "is used as a reagent for the ELISA tests and reacts with free toxin in both the first test and the second test." The first test contains free toxin as described and the antibody reacts with that free toxin.

Second paragraph rejections of claim 15

Claim 15 stands rejected on the basis (a) that the word "novel" lacks antecedent basis and (b) that the term "non-immunological binding" lacks clarity. As to point (a), "novel" has been deleted from the claim. As to point (b), the term is intended to point out that while LTNF binds with toxins, it is not an antibody and does not bind the toxin in the manner of an antibody. Sanchez recognizes this fact is true as well for the factors he was working with. At page 1452, near the bottom of the page, Sanchez states: "These antihemorrhagic factors are not antibodies since they have different physical properties and do not show protolytic activity." The term is therefore submitted to be in compliance with 35 USC 112.

Reconsideration and withdrawal of the 35 USC 112 rejections is requested.

Rejections under 35 USC 102

Claims 11-13 stand rejected under 35 USC 102(b) as being anticipated by Sanchez et al 1998, Toxicon: 36: 1451-1459 in light of Farah et al 1996, Toxicon: 34: 1067-1071, on the basis that "the monoclonal antibodies disclosed by Sanchez et al read on the claimed composition". It is noted that this rejection is highly unusual in that two references are being combined to make a 35 USC 102 rejection and that the analysis of what "reads on what" is reversed. As pointed out below, Sanchez is also not a proper 35 USC 102(b) reference against the instant claims, and it is requested that the examiner point to the section and part of 35 USC 102 that is being relied upon

in the event that the current rejections over Sanchez are maintained, or new ones made.

Sanchez discloses a composition identified as DV-2LD#2 antibody. The composition which this antibody is made against is not fully characterized. However, the DV-2LD#2 antibody is not reactive directly against venom as disclosed at the bottom of page 1454 of Sanchez and the composition discovered by applicant possesses this property and claim 13 recites it, so at least claim 13 distinguishes. Furthermore, claim 11 recites "IgG antibody made against a peptide consisting of five to ten amino acids from the N-terminal of SEQ ID NO: 1 in the absence of carrier protein molecule" and Sanchez produced the antibodies disclosed therein against proteins. There is not reasonable basis for the position that IgG antibody produced against proteins would be the same as IgG antibody produced against peptide, especially since the toxin binding properties of the antibodies are different.

Farah is pointed to in an attempt to show that the antibodies of Sanchez are inherently made against the same substances recited in claim 14. However, the amino acid sequence which has identity with the sequence recited in claim 14 is a factor from D. marsupialis. Sanchez sampled from Virginia opossum, and Farah sets forth a sequence in the same table for a factor from D. virginia which differs from the recited sequence at positions 6, 9 and possibly 13-15. Farah is totally silent as to antibody formation. Claim 11 is furthermore close ended to use of a 5-10 amino acid peptide as the antigen, and neither of the references nor their combination discloses or suggests use of peptide of an antigen.

Farah thus does not support an inherency type of anticipation rejection based on Sanchez. Selection is an obviousness question (The claimed invention furthermore goes beyond mere selection by use of a peptide rather than a protein). Reconsideration and withdrawal of the anticipation rejection is therefore requested. In the event that the rejection is repeated, and identification of the portion of 35 USC 102 being relied upon is requested.

Rejection under 35 USC 103

Claims 5, 7-8 and 14-16 stand rejected under 35 USC 103(a) as being unpatentable over Sanchez et al 1998, Toxicon: 36: 1451-1459 in view of Harlow and Lane 1988.

Sanchez et al was apparently published in October, 1998 (a copy of ScienceDirect web pages are attached) and thus Sanchez is not a proper 35 USC 102(b) reference against the present application, which was filed April 27, 1999.

At page 1453, Sanchez describes "binding antihemorrhagins found in Virginia opossum serum to hemorrhagins in snake venoms." Near the bottom of page 1452, Sanchez states that the opossum antihemorrhagins "are not antibodies since they have different physical properties and do not show proteolytic activity." The resulting complex is then "detected by DV-2LD#2 antibody which is specific for Virginia opossum serum." In the language of applicant's specification, Sanchez is bringing together a toxin plus a neutralizing factor to form a complex, and the complex is then reacted with an antibody made against the neutralizing factor for the detection. The discussion relating to CAH antibody, which is made against hemorrhagic fractions of C. atrox venom, is not believed relevant, except to the extent it shows that antibodies will sometimes react with fractions they were not made against. The assertion in the office action that DV-2LD#2 antibody is "made against anti-hemorrhagins comprising N-terminal sequence of LKAMDPTPPLWIKTE" is not supported by the cited disclosures. No where does Sanchez describe the sequence, and on page 1458, referencing Catanese and Kress (1992) and (1993) Sanchez confirms that Virginia opossum serum appears to contain more than one factor that with reacts with venom.

In claims 5, 14 and 19, antibody made against the applicant's neutralizing factor is brought directly together with the toxin to produce an immunological reaction. When Sanchez combined his DV-2LD#2 monoclonal antibody directly with toxins, no reaction was observed. Sanchez states, at page 1454 in describing Figure 1(c) "When no Virginia opossum [stet. serum] was used, the 14 venoms did not react with DV-2LD#2 monoclonal antibody" and at page 1455, in

describing results "The DV-2LD#2 monoclonal antibody did not react with the same venoms when the Virginia opossum serum was excluded." In Sanchez, the DV-2LD#2 antibody is reacting with something it was made against. i.e., the neutralizing factor from the opossum serum, albeit in bound form . In claims 5, 14 and 19 the recited antibodies are reacting with something they were not not made against. Sanchez is thus neither anticipatory nor suggestive of claims 5, 14 and 19.

There is nothing in Harlow and Lane which remedies the deficiencies of Sanchez with regards to claims 5, 14 and 19. The cited portions all require use of an antibody that will bind to the antigen. The invention employs antibodies that in foresight could not reasonably be expected to bind to the recited antigens because they were not made against them.

The present amendment breaks apart the peptide and natural LTNF embodiments of the invention previously recited in claim 5. Claim 5 is now limited to the peptide embodiments, whereas claim new claim 19 is limited to the natural LTNF embodiments. Support for the additional characterizing features of natural LTNF added as limitations in claim 20 are found at page 4, line 31 through page 5, line 3 of the specification as filed, and the arguments made above apply equally to new claim 19. Also, a new claim 18 has been added which limits the claim 14 invention to the synthetic peptide embodiment. New claim 18 is fairly supported by claim 5, for example.

Portions of Harlow and Lane previously of record in the application further support the nonobviousness of what is now set forth in claims 5 and 18. Page 74, second paragraph, states:

> "Because of their size, peptides may not be immunogenic on their own. To elicit an antibody response directly, they must contain all of the features of any immunogen, notably they must have an epitope for B-cell binding and a site for class II-T-cell receptor binding. Some peptides, even surprisingly small ones, contain both these sites (or more properly, one sequence that can serve both functions), and these peptides can be used without carriers [cites omitted]. Unfortunately, there are no methods, short of immunization, to test this, and therefore, most peptides are coupled to carrier proteins before injection."

At page 75, first paragraph, Harlow and Lane disclose

> "...preparing anti-peptide antibodies is still an empirical exercise. What works well for one immunogen may fail completely for another."

The instant specification as filed further contains a discussion of haptens along the same lines as Harlow and Lane.

Since claims 5 and 18 are limited to an anti-LTNF made against a synthetic peptide consisting of at least five amino acids of SEQ ID NO: 1, these claims are now close ended and the uncertainties of antibody formation against such peptide expressed above in Harlow and Lane are fully applicable.

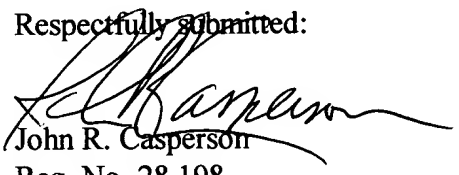
Claim 7-8 distinguish the combined references on essentially the same basis as claim 5. Claims 15-16 distinguish the combined references on essentially the same basis as claim 14.

In view of the foregoing amendment and remarks, reconsideration and withdrawal of the 35 USC 103 rejection is requested.

Conclusion

In view of the foregoing, reconsideration and withdrawal of all grounds of rejection and early notice of allowance is respectfully solicited.

Respectfully submitted:



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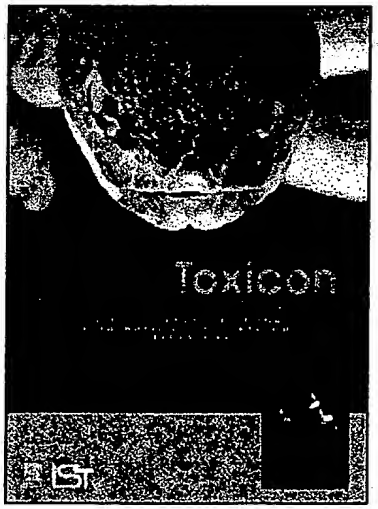

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